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Blood pressure, left ventricular hypertrophy and long-term prognosis in hemodialysis patients

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Blood pressure, left ventricular hypertrophy and long-term prognosis in hemodialysis patients. Cardiovascular events are the main cause of death in patients with chronic renal failure who are treated with hemodialysis. Hypertension is frequent among dialysis patients and may be a major cause of mortality, although epidemiological studies are controversial in this regard. This disparity in results may be the consequence of an inadequate definition of hypertension in dialysis patients as well as the interaction with hypertension with other risk factors such as malnutrition or left ventricular hypertrophy (LVH), which are strong predictors of death. Although the goal of blood pressure in dialysis has not been established yet, it seems that predialysis blood pressure levels lower than 150/90 mm Hg must be achieved for patients to avoid complications. LVH is very frequent among dialysis patients and starts early in the progression of chronic renal failure. Hypertension is the main cause for its development, but other potentially reversible factors such as anemia, volume overload, secondary hyperparathyroidism, dose of dialysis or malnutrition may also be implicated. Hence, an adequate management of patients on hemodialysis must include the strict control of blood pressure, preferably with angiotensin converting enzyme (ACE) inhibitors, together with those early measures in order to avoid the development of the other causes of LVH or to treat them when they already exist.

Patients on chronic hemodialysis have an age-adjusted death rate 3.5 times higher than the general population [1]. This poor prognosis can be explained by their high comorbidity [2, 3]. Cardiovascular events are the main cause of death, 54% among hemodialysis patients in USA [2] and 47% in Europe (Valderrábano et al, this issue). Arteriosclerosis is more frequent, severe and appears early in these patients [4]. Hypertension has been shown to be a strong predictor of mortality in general population [5]. It has generally been accepted that the blood pressure (BP) linked to a low cardiovascular risk is that lower than 120/80 mm Hg [6] and in this sense, about 80% of patients on hemodialysis have a BP higher than this level [7]. All these data suggest that hypertension would be a major cause of mortality in dialysis patients, however, the results of epidemiological studies are controversial.

Some published studies show a direct relationship between both systolic and diastolic predialysis BP and the mortality rate [8–11]. Antihypertensive therapy improves the one-year mortality rate irrespective of the level of BP control [12]. Sometimes it is necessary to look for the association of several cardiovascular factors, such as hypercholesterolemia, systolic BP, and cigarette smoking, to find a relationship with the mortality rate [13]. Moreover, hypertension has been implicated in the development of left ventricular hypertrophy (LVH) [3], arteriosclerosis [4] and ischemic cardiomyopathy [14]. In contrast, other authors show that high BP is not an independent risk factor of death [15–18], even among diabetic patients [19]. Greaves and Sharpe found an inverse relationship between predialysis diastolic BP at the beginning of hemodialysis therapy and the gross mortality rate [1]. These authors also describe that malnourished patients often have a low diastolic BP, suggesting that nutritional factors would be a strong predictor of mortality in dialysis patients [1, 20]. Moreover, an inverse relationship between BP and mortality rate has also been described to be a result of congestive heart failure [3]. Only 6.6% of long-term surviving patients on hemodialysis have a systolic BP lower than 110 mm Hg [21], and a systolic dysfunction must be suspected in these cases.

In our experience, neither systolic or diastolic BP are independent risk factors of death in hemodialysis patients. A study of survival cofactors in a cohort of 193 patients with more than six months on hemodialysis was performed. The clinical and demographic characteristics of the patient cohort at six months of patient entry on hemodialysis are shown in Table 1. Patients were evaluated at six months from the onset of hemodialysis and the results were related with the outcome data after a mean period of 81 ± 65 months. At the end of the study, 82 patients had died, 11 were lost to follow-up, and 100 were alive on treatment. Seventy-three percent of them were on hemodialysis with low permeability and compatible membranes, and the remaining patients used high performance membranes.

Key words: hypertension, left ventricular hypertrophy, cardiac complications of dialysis, hyperparathyroidism, adequacy of dialysis, anemia.

Table 1. Characteristics of the study population

Age *years*	60 ± 15 (19–85)
Male/female %	60/40
Cause of chronic renal failure %	
Diabetes mellitus	19
Primary glomerulonephritis	16
Secondary glomerulonephritis	6
Polycystic disease	8
Nephroangiosclerosis	6
Other etiology	16
Unknown disease	11
Predialysis blood pressure *mm Hg*	144/79 ± 21/12.5
Postdialysis blood pressure mm Hg	125/71 ± 23/13
Patients with antihypertensive therapy %	32
LVH in echocardiography (168 pat) %	88
Evaluated parameters were	
PCR *g/kg/day*	1.02 ± 0.29
Kt/V (Daugirdas II)	1.09 ± 0.25
Relationship between Kt/V and PCR ($N = 192$)	$r = 0.424$, $P < 0.001$; PCR = 0.475 + 0.506*Kt/V
Predialysis creatinine *mol/liter*	844 ± 255
Albumin g/*liter*	41 ± 6
Total CO_2 *mmol/liter*	22.3 ± 3.6
Serum iPTH *pg/ml*	319 ± 334
Hematocrit %	30.3 ± 5.1
Hemoglobin *g/dl*	10.1 (52% with rHuEPO)
Cholesterol *mmol/liter*	5.34 ± 1.42
Triglycerides *g/liter*	1.55 ± 1.18
HDL cholesterol *mmol/liter*	0.39 ± 0.13
LDL cholesterol *mmol/liter*	1.35 ± 0.43
Body mass index kg/m^2	22.3 ± 4.4
Arm mean muscle circumference *cm*	22 ± 4

This is from a prospective cohort study of 193 patients who survived more than 6 months on hemodialysis (HD). Baseline evaluation 6 months after HD onset and posterior follow-up is 81 ± 65 months. Blood pressure pre- and post-HD average of 12 hemodialysis sessions at sixth months after the onset of HD. LVH is left ventricular hypertrophy. Values are expressed as mean ± SD.

Causes of death were: cardiovascular 27%, infectious disease 24%, dementia and cerebrovascular events 16%, unknown etiology in 12%, and malignancies 11%. In univariate analysis comparing the variables between death and survival patients, age, serum creatinine and albumin, protein catabolism rate (PCR), hemoglobin, arm mean muscle circumference (AMMC) and postdialysis systolic BP were significantly different between both groups at six months after starting dialysis. No differences were found in systolic and diastolic predialysis BP, postdialysis diastolic BP, left ventricular mass index (LVMI), Kt/V, total CO_2, PTH, serum cholesterol and triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol nor body mass index. Using Cox regression modeling, age alone, low serum creatinine and diabetes mellitus were independent risk factors of death.

The disparity in the results from the different studies may depend upon: (*a*) statistical analyses that do not clearly define the outcome risk factors for hemodialysis [22]; (*b*) interaction of hypertension with other risk factors such as malnutrition; (*c*) the controversy over an established adequate definition of hypertension in dialysis patients; and (*d*) the strong relationship between cardiovascular mortality and LVH, which is very influenced by factors other than hypertension. The last two aspects are reviewed in the next sections.

Table 2. Blood pressure (BP) pre- and post-hemodialysis (HD) and the next day (NDBP), in 40 hemodialysis patients

	Pre-HD BP	Post-HD BP	NDBP
		mm Hg	
Systolic BP	140 ± 21	120 ± 20	127 ± 20
Diastolic BP	79 ± 13	69 ± 11	73 ± 11

Data are the mean BP of the three HD sessions and at the next day in a week.

Correlations between: preHD systolic BP and systolic NDBP are $r = 0.77$, $N = 40$; PreHD diastolic BP and diastolic NDBP are $r = 0.81$, $N = 40$; Post-HD systolic BP and systolic NDBP are $r = 0.89$, $N = 40$; post-HD diastolic BP and diastolic NDBP, $r = 0.86$, $N = 40$; $P < 0.01$.

WHAT FACTORS INFLUENCE PATIENT BLOOD PRESSUE DURING HEMODIALYSIS?

When must the patient be considered hypertensive?

Hemodialysis sessions produce cyclic changes in sodium and water content that are related to BP. We studied the mean BP before and after three hemodialysis sessions from one week, and the results are compared with basal BP values obtained from the hospital during the three next days without hemodialysis (Table 2). Both predialysis and postdialysis BP had a strong relationship with basal BP, suggesting that BP obtained from a patient on hemodialysis could be an estimate of the basal BP, although the levels are different. Predialysis BP overestimated basal BP while postdialysis BP underestimated it, although the latter was closer to the basal BP value. The decrease of BP during hemodialysis was lesser in hypertensive patients. Postdialysis BP and the mean between pre- and post-hemodialysis BP values were more closely correlated with basal interdialysis BP. Some studies using 24- to 48-hour BP monitoring confirm these concepts [23]. LVH is better correlated with predialysis systolic BP [23] and nocturnal systolic BP. The loss of a BP circadian rhythm is frequently found in these patients, and more accentuated in hypertensive patients and those with volume overload [24, 25].

Blood pressure in hemodialysis patients depends mainly on the hydration state [26–28]. In our experience, BP does not change significantly throughout the first four years on hemodialysis (Table 3). There is no relationship between the interdialysis weight gain and the predialysis BP. Hypertensive patients do not seem to have a higher weight gain, although predialysis BP in each patient does have a good correlation with the weight gain. After the week's end, BP tends to be higher and is related with a higher weight gain. An increase of BP at the end of a hemodialysis session was found in 7% of all the sessions during a three month period in 40 patients. It could be related to a sympathetic reaction

Table 3. Blood pressure (BP) and interdialytic weight gain (IGW) in 40 patients during the first four years on hemodialysis

	Pre-HD BP *mm Hg*	Dry weight *kg*	Interdialytic weight gain *g*
4th T–first year	141 ± 21/79 ± 14	60 ± 10.1	1863 ± 965[a]
4th T–2nd year	143 ± 23/80 ± 13	60 ± 10.7	2159 ± 800
4th T–3rd year	144 ± 22/80 ± 12	60.5 ± 11.1	2185 ± 847
4th T–4th year	144 ± 24/79 ± 12	60.9 ± 11.4	2064 ± 796

Data are the mean of BP and interdialytic weight gain of all sessions during last trimester (T). No significant relationship was found between BP and IWG in the group, but in each patient.

[a] $P < 0.05$ vs. 2nd, 3rd and 4th year after beginning HD

Table 4. Changes in left ventricular dimensions and function after dialysis ($N = 12$)

	LV before dialysis	LV after dialysis	*P*
LVEDD *mm*	49.4 ± 8.3	42.1 ± 9.0	< 0.05
IVST *mm*	11.4 ± 2.4	11.6 ± 2.1	NS
LVPWT *mm*	11.9 ± 2.3	11.9 ± 1.1	NS
LVMI g/m^2	134.2 ± 41.0	105.9 ± 37.5	< 0.05
E WAVE *cm/sec*	95.6 ± 31.4	70.5 ± 22.4	< 0.05
A WAVE *cm/sec*	86.1 ± 20.0	78.9 ± 19.4	NS
% Shortening	33.7 ± 14.9	35.9 ± 14.6	NS
Ejection fraction	45.9 ± 16.4	48.7 ± 15.5	NS

Mean weight loss was 2.1 ± 0.6 kg. Abbreviations are: LVEDD, left ventricular end diastolic diameter; IVST, interventricular septum thickness; LVPWT, left ventricular posterior wall thickness; LVMI, left ventricular mass index.

in response either to an exaggerated ultrafiltration or to the antihypertensive agent's clearance by dialysis.

With all the previous arguments, it is difficult to establish which BP measurement has the higher prognostic value. No matter which method of measurement is used, however, several measurements of BP must be taken, and when it is higher than 150/90 mm Hg, the diagnosis of hypertension must be considered in that patient.

The prevalence of hypertension in hemodialysis patients is very different in the literature, ranging from 2 to 58% [9, 24]. In Tassim, France, with its longer duration of hemodialysis sessions and a Kt/V > 1.5 (mean 1.7), the prevalence of hypertensive patients is around 2% [8]. In our study, 28% of the patients had predialysis systolic BP higher than 150 mm Hg and 12% had diastolic BP higher than 90 mm Hg. Postdialysis measurements showed that 10% of the patients had systolic hypertension and only 1% had diastolic hypertension. Cheigh et al found that 58% of patients had systolic and 39% diastolic hypertension. These authors suggest that hypertension is not adequately controlled in hemodialysis patients because it is not an easy task [24]. Differences in the prevalence of hypertension found among the various studies are likely due to patient characteristics such as race, social and economic status, and etiology of CRF, but the characteristics of hemodialysis and an inadequate sodium balance are highly implicated.

LEFT VENTRICULAR HYPERTROPHY IN HEMODIALYSIS PATIENTS

Left ventricular hypertrophy (LVH) is a compensatory response of the left ventricle to increase hemodynamic load. This structural abnormality includes two patterns: concentric LVH, where the cause is a cardiac afterload due to hypertension, which induces a lateral expansion of cadiomyocytes as well as proliferation of fibroblasts. The second pattern is the excentric LVH, a response to cardiac overload from anemia, arteriovenous fistula or volume overload, which results in an elongation of the myocyte. LVH is also accompanied by a reduced capillarization with a decrease in O_2 diffusion [29, 30].

The prevalence of LVH among hemodialysis patients is very high [31]. It can appear very early in the progression of CRF and may be present at the start of dialysis treatment [32, 33]; LVH is an independent risk factor of death in patients on dialysis [32, 34]. Actually, about one-half of the deaths of dialysis patients are due to cardiovascular events [2], which strongly implicates LVH as a primary risk factor [17].

Some direct consequences of LVH include poor tolerance to ultrafiltration on hemodialysis, congestive hearth failure, arrhythmia, angina pectoris and myocardial infarction, all of which may contribute to a high cardiovascular mortality [17, 29, 35–37].

RISK FACTORS FOR LEFT VENTRICULAR HYPERTROPHY

Hypertension is the main cause for the development of LVH [3, 32, 38–40], but other potentially reversible factors such as anemia, volume overload, secondary hyperparathyroidism, uremia, dose of dialysis, and malnutrition may have an important role in its pathogenesis [41].

Anemia

Typically, anemia in CRF patients on dialysis is accompanied by an hyperdynamic state with an increase in cardiac output and LV volume overload, which are directly related with the development of LVH [42, 43]. This process may induce a loss of myocardial contractility and contribute to LV dysfunction. Moreover, anemia is an independent risk factor for cardiac morbidity and mortality in ESRD patients [39, 44].

Partial correction of anemia with recombinant human erythropoietin (rhEPO) is associated with a decrease in LVH, especially due to a reduction in LV end diastolic diameter that is independent of age [45, 46]. Radermacher and Koch reviewed fifteen published studies, including patients who were treated with rhEPO during a mean time of 45 weeks. A partial correction of anemia to a steady-state hematocrit of 32.9% was obtained, which resulted in approximately an 18% decline in the LV mass index [47]. However, the improvement of LV mass did not reach

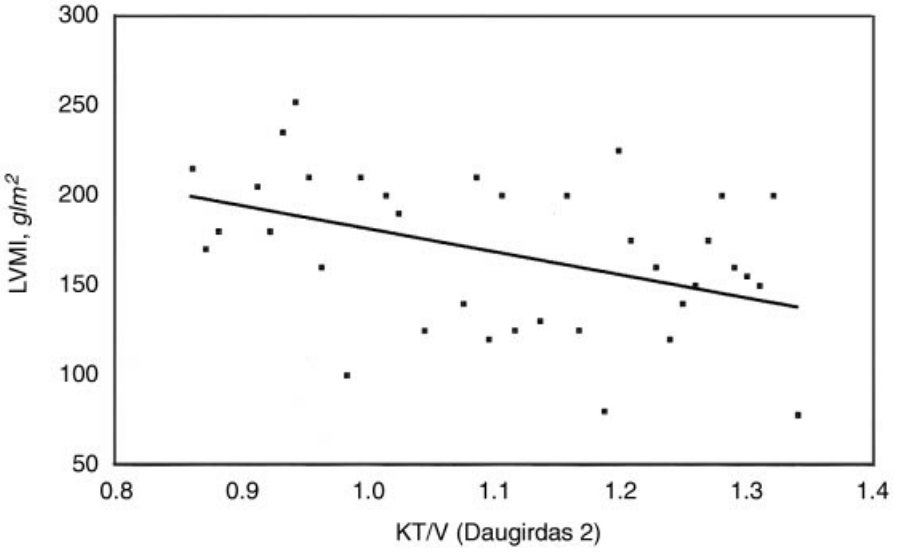

Fig. 1. Relationship between left ventricular mass index (LVMI) and Kt/V (Daugirdas 2) in 37 patients on hemodialysis ($r = -0.39$; $P = 0.01$)

normal values, suggesting either that this event was a multifactorial etiology where anemia was only a partial responsible factor, or that the hematocrit obtained was not sufficient for a complete normalization of LVH.

Beneficial effects of rhEPO therapy on LV mass may be counteracted by an increase in systemic vascular resistance, which may produce hypertension and cardiac overload [48, 49]. Withdrawing rhEPO therapy is followed by an increased in LV mass index and cardiac output with a decrease in peripheral vascular resistance [50], which confirms the role of rhEPO on the cardiac hemodynamics.

Volume overload

Salt and water retention is not only the major factor implicated in dialysis hypertension [28, 51, 52], but it may have a direct hemodynamic effect of increasing the cardiac preload. Echocardiographic findings show that interdialysis weight gain is accompanied by an increase in LVMI, mainly due to a rise in LV end diastolic diameter, which may have a long term effect on the development of LVH. Table 4 shows the changes in LV dimensions and function in 12 patients studied before and after a midweek hemodialysis session, with a mean weight loss of 2.1 kilograms.

Secondary hyperparathyroidism

Hyperparathyroidism (HPTH) is a common complication of CRF patients. It can be present very early in the decline of renal function, but mainly is found when an adequate control of calcium-phosphorous metabolism is not performed. In experimental models, it has been shown that parathyroid hormone (PTH) leads to cardiac fibrosis [53, 54] throughout the cardiac receptors for PTH in cardiac fibroblasts and myocardiocytes [55]. The relationship between HPTH and cardiac dysfunction is controversial [40, 56–58], but HPTH produces an increase in cytosolic free calcium that may result in chronotropic and inotropic effects on the myocardial cells [59, 60]. Together with other factors these changes may contribute to cardiac hyperthrophy [40, 57, 61]. In addition, a calcium phosphate deposition on the coronary microcirculation and atherosclerosis induced possibly by HPTH can predispose the patient to ischemic cardiomyopathy [62].

Until now, it has not been shown that a decline in serum levels of PTH after calcitriol treatment would be associated with an improvement of LVH. We did not find a significant relationship between PTH levels and LVMI in a group of 37 patients on hemodialysis. However, severe HPTH may play a certain role in the genesis of LVH. In this regard, we studied 12 patients on hemodialysis before and six months after total parathyroidectomy, using echocardiography. LVMI decreased significantly, which overall was due to a lower LV end diastolic diameter, but we also found an increase in hematocrit. Hence, these findings could not explain the true influence of the decrease in PTH levels *per se* on the cardiac hypertrophy, because the beneficial effect could partially be explained by the improvement of anemia [63].

Dialysis dose

There is some direct evidence that the dialysis dose is inversely related with both gross and cardiovascular mortality in hemodialysis patients [64–66]m and directly related with an improvement in cardiac structure abnormalities and dysfunction [67]. We studied 37 normotensive patients who had no previous ischemic heart disease, valvular disease or specific heart treatment. Patients were classified into two groups according to a Kt/V higher or lower than 1.1. We found a significant correlation between LV end diastolic diameter and Kt/V. A higher prevalence of LV dilation was also found in the group

with the lower dose (36% vs 5%, $P < 0.005$). Moreover, Kt/V correlated to LVMI (Fig. 1). There were no differences in systolic function in the two groups, while diastolic dysfunction was more frequently found in the group with Kt/V < 1.1 (81.2% vs 38.0%, $P < 0.01$). The logistical regression model showed a significant association between lower dialysis dose and diastolic dysfunction (OR = 6.36; $P = 0.02$) independently from LVH. Thus, the dialysis dose must be considered to be a uremic cardiomyopathy-related factor in hemodialysis patients [68].

Malnutrition

Hypoalbuminemia has been independently related to both relative risk of death and LV dilation in dialysis patients [16, 20, 32, 38, 64, 69]. It also predisposes the patient to the development of both *de novo* congestive heart failure and *de novo* ischemic heart disease [37, 70]. This association may partially explain the adverse effect that malnutrition has on the survival, although the closed mechanism is not yet clarified.

MANAGEMENT OF ARTERIAL HYPERTENSION AND LEFT VENTRICULAR HYPERTROPHY

The management of cardiovascular problems of end-stage renal disease (ESRD) patients must be attended to carefully to prevent all of the risk factors and manifestations. Hypertension must be controlled in patients on hemodialysis to avoid an impairment of tolerance to dialysis and the risk of malnutrition. BP control needs to be associated with the treatment as well as to other factors implicated in the development of LVH, such as hyperparathyroidism, hypoalbuminemia and anemia. These measurements must be started early in the treatment and progression of CRF, to avoid the reported high prevalence of cardiovascular manifestations at the onset of dialytic therapy [32].

When both an adequate dose of hemodialysis, with a Kt/V higher than 1.2, and a sodium and fluid restriction are obtained, the number of hypertensive patients on hemodialysis should be very low. Then, these patients should be monitored each 48 hours to evaluate the characteristics of their BP profile.

Strict BP control in conjunction with antihypertensive therapy, including ACE inhibitors, calcium channel blockers and beta blockers, may induce a regression of LVH [71]. However, the reduction of LVMI after the antihypertensive therapy may not only be due to a better control of BP, because some drugs (such as ACE inhibitors) can result a decrease in angiotensin II levels, which has been shown to have a proliferative effect on cardiac fibroblasts and myocardiocytes, independently of the antihypertensive and hemodynamic effects of this group of drugs [72, 73]. In this sense, Cannella et al recently showed the beneficial effect of lisinopril on decreasing the LVMI in ten normotensive patients on hemodialysis [74]. However, more studies are required to determine both the best target BP and the most appropriate antihypertensive agents in hemodialysis patients.

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